Three-component condensation in the synthesis of substituted tetrahydropyridinethiolates*

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Multicomponent cyclocondensation of Meldrum´s acid, 2-chlorobenzaldehyde, and *N*-(4-bromophenyl)-3-amino-3-thioxopropanamide in the presence of *N*-methylmorpholine afforded *N*-methylmorpholinium 3-[*N*-(4-bromophenyl)carbamoyl]-4-(2-chlorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate in 65% yield. When treated with dilute HCl, the thiolate easily transformed into *N*-(4-bromophenyl)-4-(2-chlorophenyl)-2-oxo-6-thioxopiperidine-5-carboxamide, which reacted with alkyl halides to give products of regioselective *S*-alkylation in high yields.

Key words: multicomponent condensation, Meldrum´s acid, *N*-(4-bromophenyl)-3-amino-3-thioxopropanamide, 2-oxo-1,2,3,4-tetrahydropyridine-6-thiolate.

Earlier, we developed a convenient method for preparation of functionalized tetrahydropyridines by cyclocondensation of aldehydes, cyanothioacetamide, and Meldrum´s acid (**1**) and studied their structures in detail.[1—3] Our further investigation into the synthesis of partially hydrogenated pyridines was devoted to a three-component reaction of acid **1**, 2-chlorobenzaldehyde (**2**), and monothiomalonamide derivative **3**. The last compound is a representative of methylene-reactive reagents, whose synthetic potential has been employed only partially to date.[4,5]

We found that the reaction of Meldrum´s acid **1**, aldehyde **2**, and *N*-(4-bromophenyl)-3-amino-3-thioxo-

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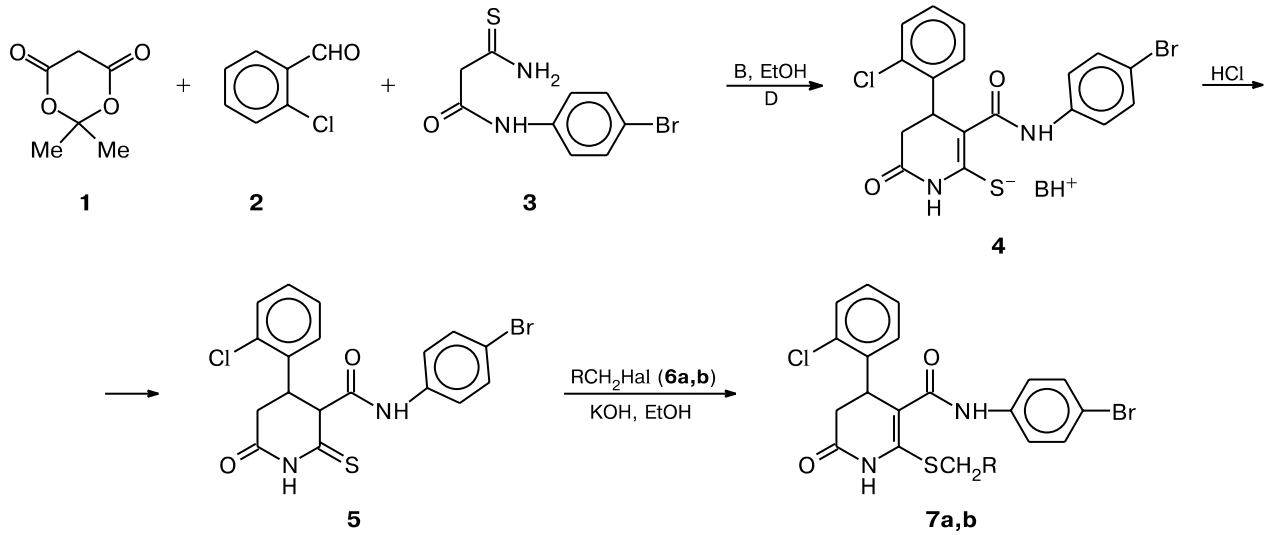
Scheme 1



1 **2** **3** **4** **5** **7a,b**

R = H (**6a**, **7a**), $CH_2C(O)NHCH_2Ph$ (**6b**, **7b**); Hal = I (**6a**), Cl (**6b**); B is *N*-methylmorpholine

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propanamide (**3**) in boiling ethanol in the presence of *N*-methylmorpholine leads to earlier unknown tetrahydropyridinethiolate **4**. Acidification of a suspension of thiolate **4** in EtOH with 10% HCl gave the corresponding 6-oxopiperidine-2-thione derivative **5**. When treated with halides **6a,b**, the latter transformed into 1,2,3,4-tetrahydropyridines **7a,b** in high yields (Scheme 1).

The structures of compounds **4**, **5**, and **7** were confirmed by IR and ^{1}H NMR spectroscopy and elemental analysis.

As expected, the alkylation of 6-oxopiperidine-2-thione **5** is highly regioselective at the S atom. However, this radically conflicts with previous data,[6] according to which alkylation of compounds structurally similar to piperidine **5** occurs at the endocyclic N atom or yields 2,3,4,5-tetrahydropyridine derivatives. The condensation mechanism, as well as other transformations of the compounds obtained and their analogs, will be described elsewhere.

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (Nujol). Elemental analysis was performed on a Perkin—Elmer C,H,N-analyser instrument. The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in acetone—heptane (1 : 1); spots were visualized with the iodine vapor. Melting points were determined on a Kofler hot stage and are given uncorrected. Meldrum´s acid (**1**) was prepared according to a modified procedure;[7] *N*-(4-bromophenyl)-3-amino-3-thioxopropanamide (**3**) was prepared according to a general procedure.[4]

***N*-Methylmorpholinium 3-[*N*-(4-bromophenyl)carbamoyl]-4-(2-chlorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (4).** A mixture of acid **1** (1.44 g, 10 mmol), aldehyde **2** (1.14 mL, 10 mmol), compound **3** (2.73 g, 10 mmol), and *N*-methylmorpholine (1.65 mL, 15 mmol) in EtOH (25 mL) was refluxed for 6 h. The resulting solution was filtered through a paper filter, concentrated to half the initial volume, and allowed to stand at ~20 °C for 24 h. The light yellow crystalline precipitate was filtered off and washed with acetone to give thiolate **4** (3.50 g, 65%), m.p. 127—132 °C. Found (%): C, 52.02; H, 4.70; N, 7.83. $C_{23}H_{25}BrClN_3O_3S$. Calculated (%): C, 51.26; H, 4.68; N, 7.80. IR, ν/cm^{-1}: 3440, 3190 (NH); 1665, 1650 (C=O). ^{1}H NMR, δ: 2.54 (m, 4 H, superposition of signals for MeN and one of the $H_2C(3)$ protons); 2.67 (dd, 1 H, $H_2C(3)$, ^2J = 16.0 Hz, ^3J = 7.3 Hz); 2.83 and 3.70 (both m, 4 H each, $(CH_2)_2N$ and $(CH_2)_2O$); 4.81 (br.d, 1 H, C(4)H); 7.15—7.58 (m, 8 H, $(C_6H_4)_2$); 7.82 (s, 1 H, C(O)N<u>H</u>Ar); 13.51 (s, 1 H, NH).

***N*-(4-Bromophenyl)-4-(2-chlorophenyl)-2-oxo-6-thioxopiperidine-5-carboxamide (5).** A suspension of thiolate **4** (2 g, 3.7 mmol) in 50% EtOH (15 mL) was treated with an excess of 10% HCl to pH 2. The resulting mixture was stirred at ~20 °C for 24 h. The precipitate that formed was filtered off to give compound **5** (1.4 g, 86%) as a white powder, m.p. 134—137 °C (EtOH—H_2O). Found (%): C, 49.65; H, 3.19; N, 6.46. $C_{18}H_{14}BrClN_2O_2S$. Calculated (%): C, 49.39; H, 3.22; N, 6.40. IR, ν/cm^{-1}: 3350—3120 (NH); 1710, 1660 (C=O). ^{1}H NMR, δ: 2.82, 3.04 (both m, 1 H each, $H_2C(5)$); 4.19 and 4.31 (both m, 1 H each, C(3)H and C(4)H); 7.16—7.44 (m, 8 H, $(C_6H_4)_2$); 10.39 (s, 1 H, C(O)N<u>H</u>Ar); 12.60 (s, 1 H, NH).

Tetrahydropyridines 7a,b (general procedure). A 10% solution of KOH (1.2 mL, 2.3 mmol) was added to a suspension of compound **5** (1 g, 2.28 mmol) in 85% EtOH (20 mL). The resulting mixture was heated to complete homogenization and filtered and alkyl halide **6a,b** (2.3 mmol) was added. The reaction mixture was refluxed for 2 min and kept at ~20 °C for 24 h. The precipitate of compound **7a,b** that formed was filtered off and washed with EtOH.

***N*-(4-Bromophenyl)-4-(2-chlorophenyl)-2-methylthio-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (7a).** The yield was 0.85 g (82%), m.p. 255—256 °C. Found (%): C, 50.89; H, 3.60; N, 6.25. $C_{19}H_{16}BrClN_2O_2S$. Calculated (%): C, 50.51; H, 3.57; N, 6.20. IR, ν/cm^{-1}: 3240—3180 (NH); 1690, 1640 (C=O). ^{1}H NMR, δ: 2.42 (s, 3 H, SMe); 2.96 (dd, 1 H, $H_2C(3)$, ^2J = 15.9 Hz, ^3J = 7.9 Hz); 3.15 (m, 1 H, HC(5)); 4.52 (br.d, 1 H, C(4)H); 7.27—7.55 (m, 8 H, $(C_6H_4)_2$); 9.84 and 9.95 (both s, 2 H, $(NH)_2$).

***N*-(4-Bromophenyl)-2-[2-(benzylaminocarbonyl)ethyl]thio-4-(2-chlorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (7b).** The yield was 0.96 g (72%), m.p. 186—187 °C. Found (%): C, 55.80; H, 3.93; N, 7.22. $C_{27}H_{23}BrClN_3O_3S$. Calculated (%): C, 55.44; H, 3.96; N, 7.18. IR, ν/cm^{-1}: 3420—3330, 3240—3180 (NH); 1700, 1660, 1635 (C=O). ^{1}H NMR, δ: 2.80 (dd, 1 H, $H_2C(3)$, ^2J = 15.9 Hz, ^3J = 7.5 Hz); 3.19 (m, 1 H, $H_2C(5)$); 3.86 (br.s, 2 H, SCH_2); 4.44 (m, 3 H, superposition of signals for C(4)H and C<u>H</u>$_2$NH); 7.15—7.55 (m, 13 H, 3 Ar); 9.06 (t, 1 H, CH_2N<u>H</u>); 10.32 and 10.76 (both s, 1 H each, 2 NH).

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